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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,648	06/13/2001	James H. Prestegard	04342.105053	5893

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EXAMINER
CLOW, LORI A

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,648	PRESTEGARD ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *17,18 and 21-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 27 April 2002
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group I, claims 1-16 and 19-20 in the paper dated 8 December 2003 is acknowledged.

Claims 17-18 and 21-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Information Disclosure Statement

The Information Disclosure Statement filed 27 April 2002 has been considered and entered. A signed copy of PTO Form 1449 is included with this Office Action.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See, for example, page 26, line 5 and line 21.

Claim Objections

Claim 11 is objected to because of the following informalities: Claim 11 includes the acronym HSQC. Applicant is requested to please spell out the words. Appropriate correction is required.

Claim 20, step (b) contains the word "tree dimensional". This should be corrected to read three-dimensional.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 19-20 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19 recite "a method for improving the binding affinity of a ligand for a biological target". However, there is no step of improving the binding affinity in the claim. The final step is one of analysis and not improvement. Clarification is requested.

Claim 1, step (c), recites "target within **the** paramagnetic zone". There is insufficient antecedent basis for "the paramagnetic zone" in the claim. Clarification is requested.

Claim 5, step (a), recites "deducing **the** relative three-dimensional orientation". There is insufficient antecedent basis for "the relative" in the claim. Clarification is requested.

Claim 5, step (a) and step (b), recites "relative orientation". It is unclear what is meant by relative. Relative to what? Is the orientation relative to some point in space or to some other defined parameter?

Claim 5, step (b) recites "substantially". It is unclear as to the metes and bounds of the word "substantially". Does this mean that the orientation is almost in the relative position or exactly in the relative position?

Claim 20, step (c) recites "substantially". It is unclear as to the metes and bounds of the word "substantially". Does this mean that the orientation is almost in the relative position or exactly in the relative position?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 10-16, 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (Journal of Molecular Biology (1999) Vol. 287, pages 609-625; PTO Form 1449 Reference AJ).

The instant invention is drawn to a method for improving the binding affinity of a ligand for a biological target comprising preparing a first NMR spectra of a complex comprising a biological target and a parmagnetically labeled derivative, preparing a second NMR spectra of a second complex comprising a biological target and a second ligand, analyzing spectra to determine if the second ligand binds to the target in the parmagnetic zone of the paramagnetically labeled derivative.

Johnson et al. teach a method of using NMR spectroscopy (HSQC spectra) to provide structural understanding of the binding properties of CBD_{N1} and CBD_{N2} (N-terminal cellulose binding domains from *Cellulomonas fimi* cellulase CenC). The structures of CBD_{N1} and CBD_{N2} were calculated using NMR data collected for these protein domains in the presence of

concentrations of cellotetaose or cellopentaose, respectively (page 610, column 2). Derivatives of cellotriose and cellotetraose were prepared with 2,2,6,6-tetramethylpiperidine-1-oxy-4-ol (TEMPO) spin-label covalently attached to the reducing end of the sugar. TEMPO is a paramagnetic relaxation probe. The labeled sugars can be used to obtain long range distance information about the CBD-cellooligosaccharide complexes (page 610, column 2). It was determined that the modified sugars bind to CBD_{N1} and CBD_{N2} in both possible orientations. The interactions of the TEMPO-labeled cellooligosaccharides with CBD_{N1} and CBD_{N2} were analyzed by monitoring the $^{1}H^{5}$ and ^{15}N chemical shifts of the proteins upon titration with these sugars. The spectral changes were similar to those observed for the unlabelled cellooligosaccharides (page 611, column2). Perturbation effects were also studied (beginning page 612, column 1-page 613, column 1). Inspection of the HSQC spectra of the complexes provided the binding orientation of the sugars. Three-dimensional orientations were also deduced as seen in Figure 8. Multiple binding orientations were uncovered by studying the effects of the TEMPO-Glc_3 and TEMPO-Glc_4 on relaxation properties of CBD_{N1} and CBD_{N2}. Given the TEMPO-labeled sugars and the corresponding unmodified cellooligosaccharides bind the CenC CBDs with similar affinities and produce similar chemical shift perturbations, the conclusion was that Glc_3 and Glc_4 are bound in multiple orientations (see discussion) (binding elucidation).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 and 19-20 are rejected under 35 U.S.C. 103(a) as being obvious over Johnson et al. (Journal of Molecular Biology (1999) Vol. 287, pages 609-625; PTO Form 1449 Reference AJ), in view of Fischer et al. (Biochemistry (1999) Vol. 38, pages 9013-9022).

The instant invention is drawn to a method for improving the binding affinity of a ligand for a biological target comprising preparing a first NMR spectra of a complex comprising a biological target and a parmagnetically labeled derivative, preparing a second NMR spectra of a second complex comprising a biological target and a second ligand, analyzing spectra to

determine if the second ligand binds to the target in the parmagnetic zone of the paramagnetically labeled derivative.

Johnson et al. teach a method of using NMR spectroscopy (HSQC spectra) to provide structural understanding of the binding properties of CBD_{N1} and CBD_{N2} (N-terminal cellulose binding domains from *Cellulomonas fimi* cellulase CenC). The structures of CBD_{N1} and CBD_{N2} were calculated using NMR data collected for these protein domains in the presence of concentrations of cellotetaose or cellopentaose, respectively (page 610, column 2). Derivatives of cellotriose and cellotetraose were prepared with 2,2,6,6-tetramethylpiperidine-1-oxy-4-ol (TEMPO) spin-label covalently attached to the reducing end of the sugar. TEMPO is a paramagnetic relaxation probe. The labeled sugars can be used to obtain long range distance information about the CBD-cellooligosaccharide complexes (page 610, column 2). It was determined that the modified sugars bind to CBD_{N1} and CBD_{N2} in both possible orientations. The interactions of the TEMPO-labeled cellooligosaccharides with CBD_{N1} and CBD_{N2} were analyzed by monitoring the $^{1}H^{5}$ and ^{15}N chemical shifts of the proteins upon titration with these sugars. The spectral changes were similar to those observed for the unlabelled cellooligosaccharides (page 611, column2). Perturbation effects were also studied (beginning page 612, column 1-page 613, column 1). Inspection of the HSQC spectra of the complexes provided the binding orientation of the sugars. Three-dimensional orientations were also deduced as seen in Figure 8. Multiple binding orientations were uncovered by studying the effects of the TEMPO-Glc_3 and TEMPO-Glc_4 on relaxation properties of CBD_{N1} and CBD_{N2}. Given the TEMPO-labeled sugars and the corresponding unmodified cellooligosaccharides bind the CenC CBDs with similar affinities and produce similar chemical shift perturbations, the

conclusion was that Glc_3 and Glc_4 are bound in multiple orientations (see discussion) (binding elucidation).

Johnson et al. do not teach the methods of claims 7-9, which includes producing a field ordered state, which is in an aqueous dispersion of lipid bicelles and analyzing dipolar coupling. However, Fischer et al. do teach an NMR approach based upon orientational constraints derived from residual dipolar couplings that are seen in protein spectra taken in a partially oriented media (page 9013, column 2). Residual dipolar couplings can provide long-range information about domain orientation in multidomain proteins. Analysis via a matrix approach is used and dipolar data are collected on proteins oriented by inherent magnetic anisotropy or by dissolution in liquid crystal media that includes phospholipid bicelles and bacteria phage (page 9014, column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to utilize data for proteins that were oriented by bicelles, as taught by Fischer et al. in the methods of Johnson et al. Fischer et al. motivate one to do so in stating that dipolar data are collected in numerous ways, such as bicelle orientation of proteins (see above).

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (571) 272-0549.

MARJORIE MORAN
PATENT EXAMINER

February 19, 2004

Lori A. Clow, Ph.D.
Art Unit 1631